

PAT-103 5/02 PTO RECEIPT FOR INDICATED ITEMS

Atty/Agent: Aubrey A. Haddach

Application No.: Not yet assigned

Date: 04-07-04

Applicant/Inventor(s): Pantoliano et al.

C# 044988

Title: Microplate Thermal Shift Assay Apparatus for Ligand

M# 0308977

Development and Multi-Variable Protein Chemistry Optimization

ENCLOSED: EL 989434393 US

- ☐ Response to Office Action ☐ Amendment ☐ Appendix ☐ Transmittal
- ☒ New Patent Application ☐ Request for PCT # \_\_\_\_\_ No. of Pages
- # 1 No. of Pages Abstract; # 109 No. of Pages Spec & Claims
- # 42 No. Sheets Drawings (Fig(s) 1 to 42 ) ☐ 1 set Formal
- ☒ Declaration (3 #pgs) ☐ Issue and Printing Fees ☐ Certificate of Correction
- ☐ Assignment ☐ PCT Power of Attorney ☐ Change of Entity Status
- # \_\_\_\_\_ No. of Priority Documents ☐ Response to Invitation to Correct Defects
- ☐ PCT Fee Calculation Sheet (in duplicate) ☐ Petition for Extension of Time
- ☒ IDS # 5 No. of Pages ☐ cited Appl(s). ☐ Foreign sch rept./OA
- ☒ PTO-1449 ☒ cited docs. ☐ Status Letter

Other: Statement to Support Filing and Submission of Sequence Listing; Electronic Copy of Sequence Listing; Request to Approve Proposed Drawing Corrections; Preliminary Amendment and Submission of Sequence Listing; Return Post Card

22141 U.S. PTO  
10/821274





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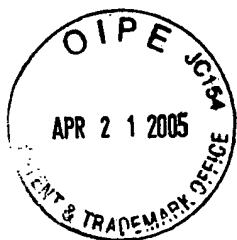
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FROM: (PLEASE PRINT)	PHONE ( )
PILLBOURY WINTHROP LLP 11062 EL CAMINO REAL STE 200 SAN DIEGO CA 92130-2072 AAH/aar 044988-0308977 Continuation Application	

TO: (PLEASE PRINT)	PHONE ( )
MAIL STOP PATENT APPLICATION Commissioner for Patents P.O. Box 1450 Alexandria, VA, 22313-1450	


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**FILE COPY**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the Patent Application of:	Group Art Unit: Not yet assigned
Applicant: Pantoliano <i>et al.</i>	Examiner: Not yet assigned
Serial No.: Not yet assigned	<u>Certificate of Mailing Under C.F.R. §1.8</u>
Filed: April 7, 2004	I hereby certify that this correspondence and all marked attachments are being deposited by Express Mail, Express Mailing Label No.: EL 989434393 US on April 7, 2004 addressed to: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
Title: <i>Microplate Thermal Shift Assay Apparatus For Ligand Development And Multi-Variable Protein Chemistry Optimization</i>	By:  Abigail Rivamonte

**PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.121**  
**AND SUBMISSION OF SEQUENCE LISTING**

MAIL STOP PATENT APPLICATION  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

The above-identified application, enclosed herewith, is filed under 37 C.F.R. § 1.53(b) as a continuing (continuation) application during pendency of parent application Serial No. 09/801,676. Prior to examination of this application and before calculations of the fees, Applicants respectfully request the that following amendments be entered:

**Amendments to the Specification** are reflected on page 2 of this paper.

**Amendments to the Drawings** are reflected on page 4 of this paper.

**Amendments to the Claims** are reflected in the listing of claims which begins on page 5 of this paper.

**Remarks** begin on page 8 of this paper.

**Conclusion** begins on page 9 of this paper.

**Amendment to the Specification:**

Please amend the specification in accordance with the following:

Delete the paragraph on page 1, beginning on line 4, and replace it with the following paragraph:

---

This application is a continuation of co-pending U.S. patent application number 09/801,676, filed March 9, 2001. U.S. patent application number 09/801,676 was filed as a continuation of U.S. patent application number 09/459,996, filed December 14, 1999 (U.S. Patent 6,214,293). U.S. patent application number 09/459,996 was filed as a continuation of 08/853,459, filed May 9, 1997 (U.S. Patent 6,903,920), which claimed priority to U.S. provisional application number 60/017,860, filed May 9, 1996, all of which are incorporated herein by reference in their entireties.

---

Amend the paragraph on page 17 beginning on line 7, as follows:

---

Figures 8A and 8B show shows the results of a miniaturized microplate thermal shift assay of aprosulate binding to the D(II) domain of human FGF receptor 1.

---

Amend the first paragraph on page 5 as shown below:

---

Like calorimetric technologies, spectral technologies have been used to monitor temperature induced protein unfolding (Bouvier, M. *et al.*, *Science* 265:398-402 (1994); Chavan, A.J. *et al.*, *Biochemistry* 33:7193-7202 (1994); Morton, A. *et al.*, *Biochemistry* 1995:8564-8575 (1995)). ~~The calorimetric and spectral thermal shift studies described above all share a common limitation. In each study, only one binding reaction was heated and assayed at a time.~~ The single sample heating and assay configuration, as conventionally performed, has impeded the application of thermal shift technologies to high throughput screening of combinatorial libraries. Thus, there is a need for a thermal shift technology which can be used to screen combinatorial libraries, can be used to identify an drank lead compounds, and is applicable to all receptor proteins.

---

Amend the paragraph starting on page 70, line 4, and ending on page 70, line 15, as shown below:

---

Using the computer controlled process DirectedDiversity® (see U.S. Patent Number 5,463,564), scientists at 3-Dimensional Pharmaceuticals, Inc. have generated a combinatorial library of compounds directed at the active site of human  $\alpha$ -thrombin. Approximately 400 compounds were synthesized and assayed by a conventional spectrophotometric kinetic assay in which succinyl – Ala-Ala-Pro-Arg-p-nitroanilide (SEQ ID NO:1) (Bachem, King of Prussia, PA) served as the substrate. Five of these compounds, which are characterized by  $K_i$ 's that span almost four orders of magnitude in binding affinity, were used to test the range and limits of detection of the thermal shift assay. These five proprietary compounds are listed in Table 3, along with the  $K_i$  for each respective compound, as measured by the kinetic assay (last column).  $K_i$ 's for these compounds ranged from 7.7 nM for 3dp-4026 to 20.0  $\mu$ M for 3dp-3811.

---

Amend the current version of the paragraph starting on page 19, line 1, and ending on page 19, line 2, to read:

---

**Figure 27** is a schematic diagram of a method of screening biochemical conditions that optimize protein folding. This method employs denatured protein tagged with H-H-H-H-H-H (SEQ ID NO: 2) or R-R-R-R-R-R (SEQ ID NO: 3).

---

Please insert the sequence listing at the end of the application.

**Amendments to the Drawings:**

Please make the following amendments to the drawings:

---

Replace FIG. 8 with FIGS. 8A and 8B, as shown in the drawings submitted with the concurrently filed Request to Approve Proposed Drawing Corrections.

---

Amend FIGS. 25 and 41A as shown in red in the drawings submitted with the concurrently filed Request to Approve Proposed Drawing Corrections.

---

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in this application.

The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Claims 1-53 have been cancelled. Claims 54-63 have been added. These amendments introduce no new matter and their entry is respectfully requested.

**Listing of Claims:**

Claims 1-53. (Cancelled).

54. (New) A method for identifying a ligand that binds to a protein, comprising the steps of:

(1) receiving unfolding data that indicates thermal unfolding as a function of temperature for a protein incubated with a molecule tested for binding;

(2) determining an unfolding temperature for the protein in the presence of the molecule from the unfolding data;

(3) comparing the unfolding temperature midpoint for the protein incubated with the ligand with the unfolding temperature midpoint for the protein in the absence of any molecules tested for binding; and

(4) determining that the molecule tested for binding binds to the protein when a difference between the unfolding temperature midpoint for the protein in the presence of the molecule and unfolding temperature midpoint for the protein in the absence of any molecules tested for binding exceeds a threshold.

55. (New) The method according to claim 54, wherein step (2) comprises the step of plotting thermal unfolding as a function of temperature for the protein incubated with the molecule, and determining the unfolding temperature midpoint for the protein in the presence of the molecule from the plot.

56. (New) The method according to claim 55, further comprising the steps of:

(5) receiving data that indicates thermal unfolding as a function of temperature for the protein in the absence of any molecules tested for binding;

(6) plotting thermal unfolding as a function of temperature for the protein in the absence of any molecules tested for binding; and

(7) determining the unfolding temperature midpoint for the protein in the absence of any molecules tested for binding from the associated plot.

57. (New) The method according to claim 54, wherein the molecule that binds is a ligand, and further comprising the step of:

(5) estimating ligand binding affinity.

58. (New) The method according to claim 57, wherein step (5) comprises the step of estimating the ligand binding affinity at the unfolding temperature midpoint.

59. (New) The method according to claim 54, wherein step (1) comprises the step of receiving fluorescence data.

60. (New) A computer program product comprising a computer useable medium having control logic embodied in said medium, for causing a computer to process thermal unfolding data, said control logic comprising:

a thermal unfolding data generating routine that causes the computer system to generate thermal unfolding data from fluorescence information received from a plurality of samples;

a thermal unfolding curve generation routine that causes the computer system to generate thermal curves from the thermal unfolding data; and

a thermal unfolding curve comparison routine that causes the computer system to compare the thermal unfolding curves.



61. (New) A computer program product comprising a computer useable medium having control logic embodied in said medium, for causing a computer to process thermal unfolding data, said control logic comprising:

    a thermal unfolding data generating routine that causes the computer system to generate thermal unfolding data from fluorescence information received from a plurality of samples;

    a thermal midpoint determining routine that causes the computer system to determine the thermal unfolding midpoint temperatures from the thermal unfolding data; and

    a thermal midpoint comparison routine that causes the computer system to compare the thermal unfolding midpoint temperatures.

62. (New) The computer program product according to claim 61, wherein said thermal midpoint determining routine comprises a thermal unfolding curve generation routine that causes the computer system to generate thermal curves from the thermal unfolding data and to determine the thermal unfolding temperature midpoints from the curves.

63. (New) The computer program product according to claim 61, wherein said control logic further comprises:

    a positioning control routine that causes the computer system to control a positioning system for the plurality of samples.

### **REMARKS**

This Preliminary Amendment is being submitted with the filing of the above-identified application, and therefore Applicants believe that this response is timely filed, and that no fees are due in connection with this submission. In the event that Applicants are incorrect in their assumption, please charge any fee due in connection with this submission to Deposit Account No. 50-2212, Order Number 044988.030.8977.

#### ***Amendments to the Specification***

The specification has been amended to direct the entry of the enclosed sequence listing after the claims of the above-identified application and to provide SEQ ID NOs next to the specific sequences. In accordance with 37 C.F.R. § 1.821(e), a computer readable copy of the sequence listing is included herewith. In accordance with 37 C.F.R. § 1.821(f), the paper copy of the sequence listing and the computer readable copy of the sequence listing submitted herewith in the above application are the same.

The amendments to the Specification are made in accordance with similar amendments in the parent case. These amendments introduce no new matter. Thus, Applicants respectfully request that the sequence listing submitted herewith be introduced into the above-identified application.

#### ***Amendments to the Drawings***

FIG. 8 is replaced with FIGS. 8A and 8B, as shown in the drawings submitted with the concurrently filed Request to Approve Proposed Drawing Corrections. Similar changes were approved by the Examiner in the parent application (Serial No. 09/801,676).

FIGS. 25 and 41A are amended as shown in red in the drawings submitted with the concurrently filed Request to Approve Proposed Drawing Corrections. Specifically, in FIG. 25, a diamond symbol and the text "pH 8/0.1 NaCl" is sought to be added and in FIG. 41A, the legend "Control ANS/No Protein" is sought to be added. Similar amendments were approved by the Examiner in the parent application (Serial No. 09/801,676).

The proposed changes add no new matter to the application. Applicants request that the Examiner approve the proposed corrections. After official communication of such approval, Applicants will make the appropriate corrections and submit revised formal drawings.

*Amendments to the Claims*

Newly added claims 54-63 are directed to data processing aspects of the present invention. Support for claims 54-63 can be found throughout the specification, for example, at page 67, line 1 through page 69, line 9, and Figures 37, 40, and 42.

Claims 54-63 substantially correspond to claims 54-58, 65, and 67-70 from the parent application (Serial No. 09/801,676). Claims 60-63 substantially correspond to non-elected claims 80-83 from the grandparent application (Serial No. 09/459,996, which issued as U.S. Patent No. 6,214,293).

Newly added claims are believed to introduce no new matter and their entry is respectfully requested.

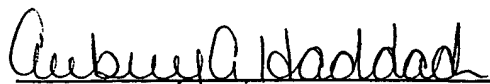
**CONCLUSION**

Applicants respectfully request that the proposed amendment be entered and the claims examined on the merits. Early and favorable consideration is requested.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

Date: April 7, 2004



Aubrey A. Haddach  
Registration No. 48,374  
PILLSBURY WINTHROP, LLP  
11682 El Camino Real, Suite 200  
San Diego, California 92130-2092  
(858) 847-4189



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

<p>In re the Patent Application of:</p> <p>Applicant: Pantoliano <i>et al.</i></p> <p>Serial No.: Not yet assigned</p> <p>Filed: April 7, 2004</p> <p>Title: <i>Microplate Thermal Shift Assay Apparatus For Ligand Development And Multi-Variable Protein Chemistry Optimization</i></p>	<p>Group Art Unit: Not yet assigned</p> <p>Examiner: Not yet assigned</p> <hr/> <p><u>Certificate of Mailing Under C.F.R. §1.8</u></p> <p>I hereby certify that this correspondence and all marked attachments are being deposited by Express Mail, Express Mailing Label No.: EL 989434393 US on April 7, 2004 addressed to: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u><i>A. Rivamonte</i></u> Abigail Rivamonte</p>
---	---

**STATEMENT TO SUPPORT FILING AND SUBMISSION OF SEQUENCE LISTING**  
**IN ACCORDANCE WITH 37 C.F.R. §1.821-1.825**

MAIL STOP PATENT APPLICATION  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

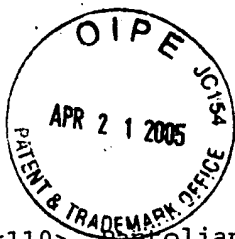
Sir:

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted in accordance with 37 C.F.R. § 1.821(c), (e), (f) and (g), or § 1.825(d) and (b), respectively, are the same.

Respectfully submitted,

Date: April 7, 2004

*Aubrey A. Haddach*  
Aubrey A. Haddach  
Registration No. 48,374  
PILLSBURY WINTHROP, LLP  
11682 El Camino Real, Suite 200  
San Diego, California 92130-2092  
(858) 847-4189



SEQUENCE LISTING

<110> Pantoliano, Michael W.  
Bone, Roger F.  
Rhind, Alexander W.  
Salemme, Francis R.

<120> Computer Program for Thermal Shift Assay Apparatus for  
Ligand Development and Multi-Variable Protein Chemistry Optimization

<130> 044988-0308977

<140> To be assigned

<141> Herewith

<150> 60/017,860

<151> 1996-05-09

<150> 09/801,676

<151> 2001-03-09

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<170> PatentIn version 3.1

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Six histidine epitope tag of  
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1 5

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In the Patent Application of:  Applicant: Pantoliano <i>et al.</i>  Serial No.: Not yet assigned  Filed: April 7, 2004  Title: <i>Microplate Thermal Shift Assay Apparatus For Ligand Development And Multi-Variable Protein Chemistry Optimization</i>	Group Art Unit: Not yet assigned  Examiner: Not yet assigned  <hr/> <p align="center"><u>Certificate of Mailing Under C.F.R. §1.8</u></p> I hereby certify that this correspondence and all marked attachments are being deposited by Express Mail, Express Mailing Label No.: EL 989434393 US on April 7, 2004 addressed to: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.  By: <u><i>A. Rivamonte</i></u> Abigail Rivamonte
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**REQUEST TO APPROVE PROPOSED DRAWING CORRECTIONS**

MAIL STOP PATENT APPLICATION  
 Commissioner for Patents  
 P.O. Box 1450  
 Alexandria, VA 22313-1450

Sir:

Attached are copies of three (3) sheets of drawings. Two of the sheets of drawings contain proposed corrections to Figures 25 and 41A, circled in red. In Figure 25, a diamond symbol and the text "pH 8/0.1 NaCl" is sought to be added. In Figure 41A, the legend "Control ANS/No Protein" is sought to be added. The third drawing sheet contains Figures 8A and 8B, which Applicants propose in place of original drawing Figure 8. Similar amendments were approved in the parent (Application No. 09/801,676).

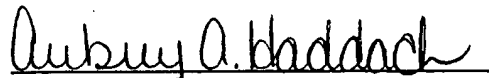
The proposed changes add no new matter to the application. Applicants request that the Examiner approve the proposed corrections. After official communication of such approval, Applicants will make the appropriate corrections and submit the formal drawings.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. No fee is believed to be due in connection with the filing of this request. However, if any fee is

due, please charge the appropriate fee to Deposit Account No. 50-2212, Order Number 044988.030.8977.

Respectfully submitted,

Date: April 7, 2004

A handwritten signature in cursive script, reading "Aubrey A. Haddach", written over a horizontal line.

Aubrey A. Haddach

Registration No. 48,374

PILLSBURY WINTHROP, LLP

11682 El Camino Real, Suite 200

San Diego, California 92130-2092

(858) 847-4189



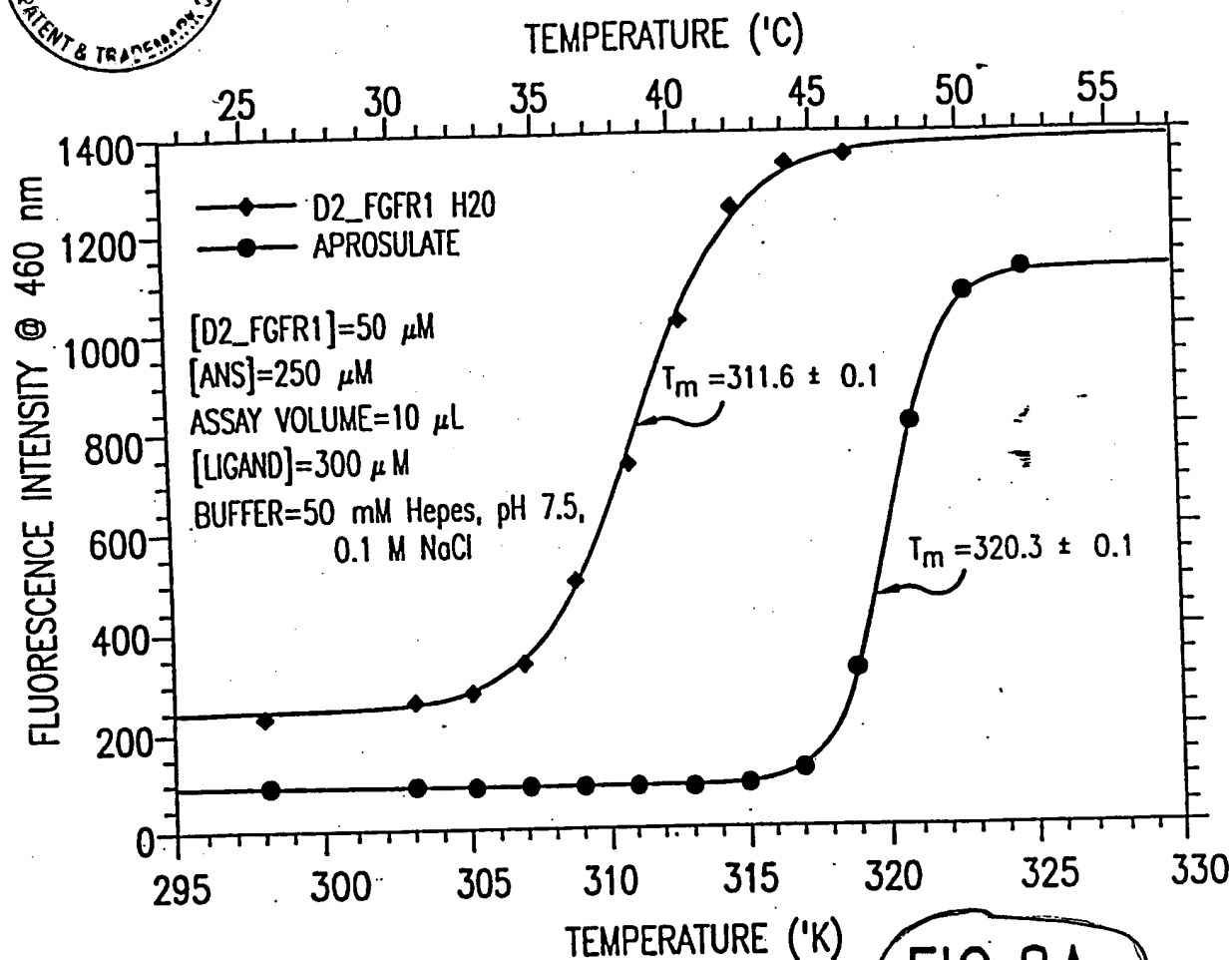
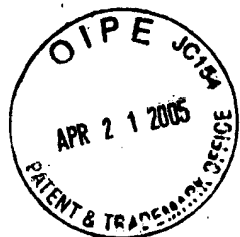
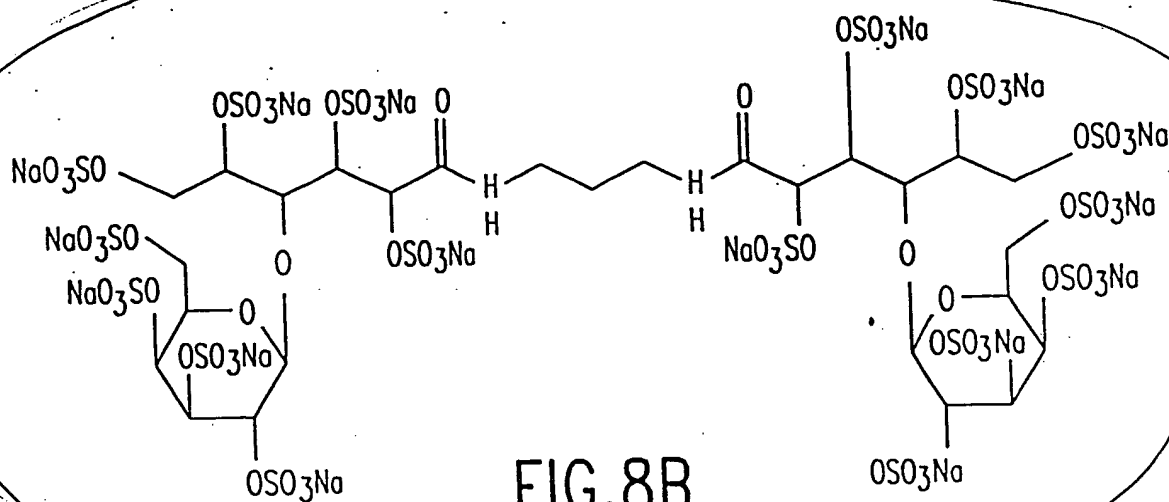
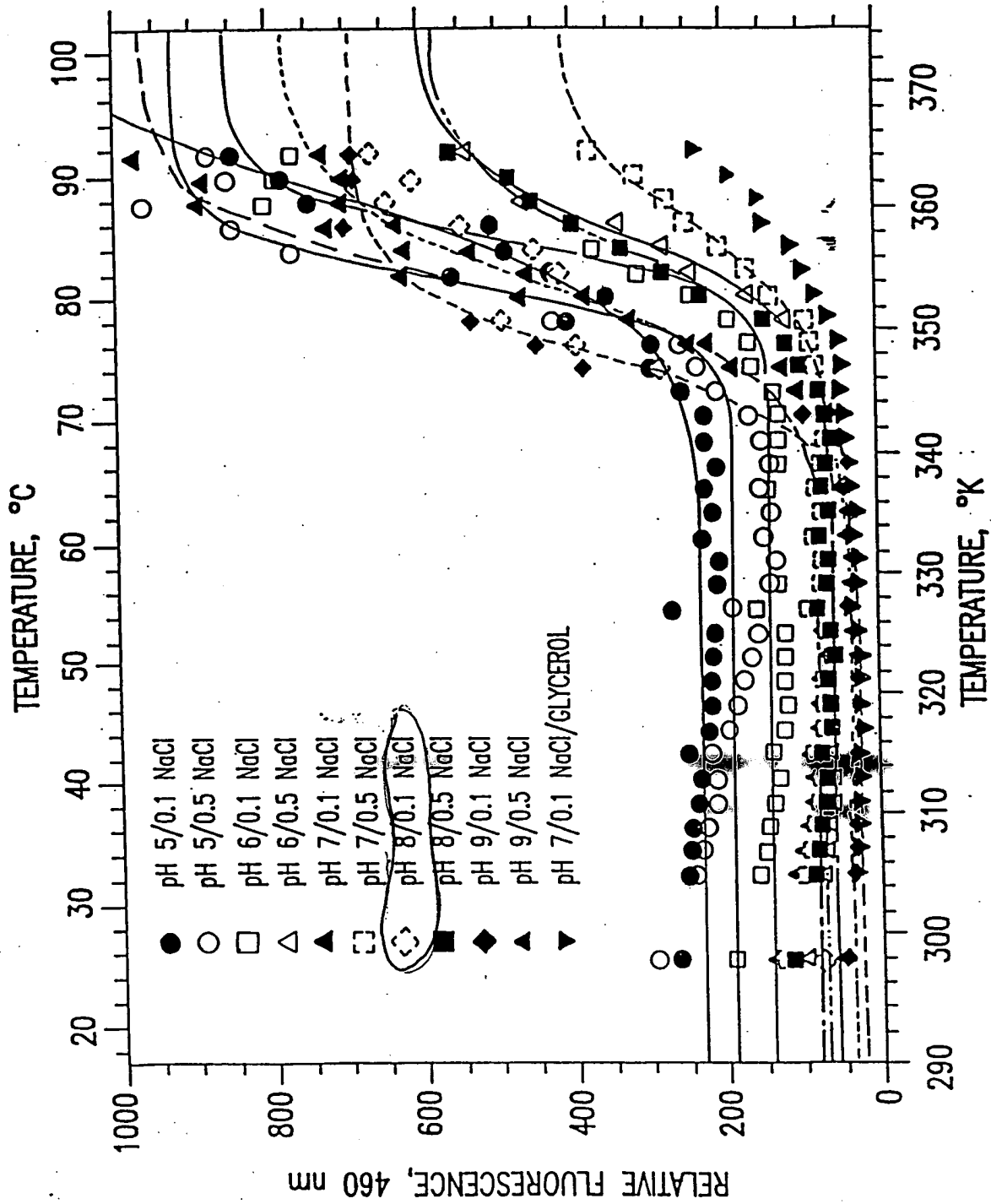


FIG.8A



Annotated maulled-up drawing

FIG. 25



Annotated marked-up  
drawings

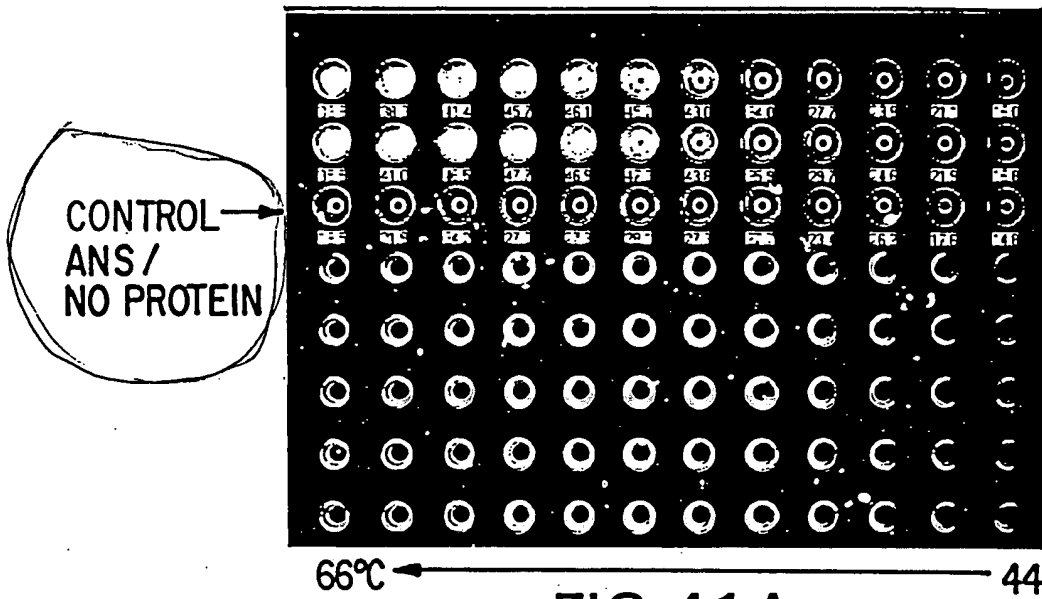


FIG.41A

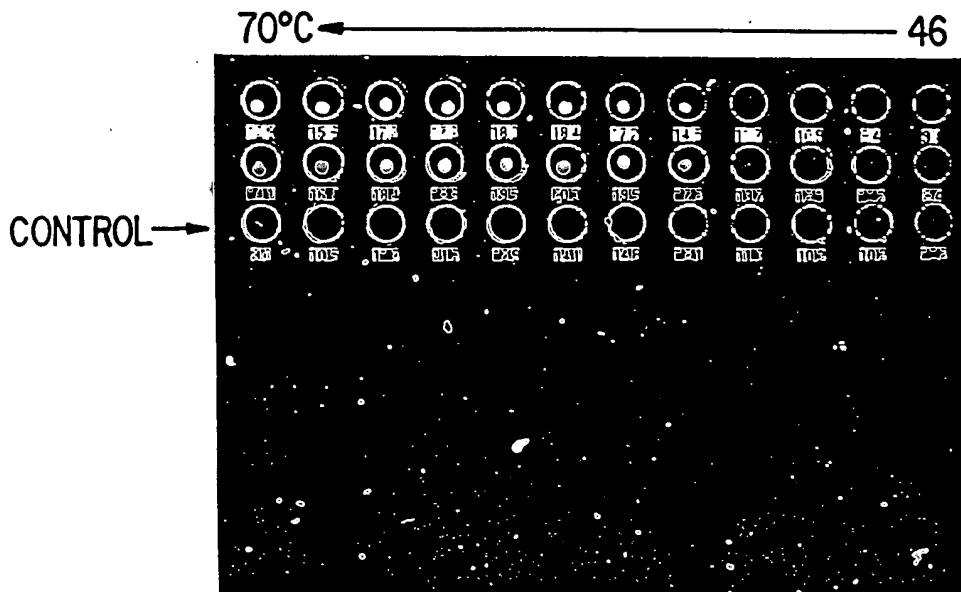
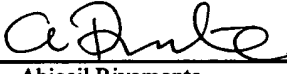


FIG.41B



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the Patent Application of:	Group Art Unit: Not yet assigned
Applicant: Pantoliano <i>et al.</i>	Examiner: Not yet assigned
Serial No.: Not yet assigned	<u>Certificate of Mailing Under C.F.R. §1.8</u> I hereby certify that this correspondence and all marked attachments are being deposited by Express Mail, Express Mailing Label No.: EL 989434393 US on April 7, 2004 addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
Filed: April 7, 2004	By:  Abigail Rivamonte
Title: <i>Microplate Thermal Shift Assay Apparatus for Ligand Development and Multi-Variable Protein Chemistry Optimization</i>	

**INFORMATION DISCLOSURE STATEMENT**

MAIL STOP PATENT APPLICATION  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. § 1.56, Applicant brings the art documents listed on the attached Form PTO-1449 to the attention of the Examiner for consideration in connection with the examination of the above-identified application.

This Information Disclosure Statement (IDS) is being filed within the period specified at 37 C.F.R. § 1.97(b). Specifically, before mailing of a first Office Action.

Copies of the following documents were cited by or submitted to the Office in an IDS that complies with 37 C.F.R. § 1.198(a)-(c) in Application No. 08/853,459, filed May 9, 1996 (U.S. Patent No. 6,036,920), which is relied upon for an earlier filing dated under 35 U.S.C. § 120: 1-5; 7-13; 15-19; 21-23; 31-33; 35; 37-39; 41-51. Thus, pursuant to 37 C.F.R. § 1.198(d), Applicants have not included copies of these references. Copies of the following documents are enclosed: 6; 14; 20; 24-30; 34; 36; 40.

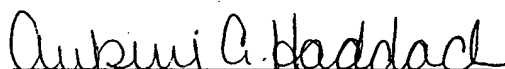
It is respectfully requested that the Examiner confirm consideration of the cited documents by initialing the attached Form PTO-1449 and returning a copy of the initialed form to Applicant.

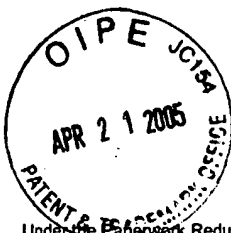
The IDS is intended to be in full compliance with the rules, but should the Examiner find any part of its required content to have been omitted, prompt notice to that effect is earnestly solicited, along with additional time under 37 C.F.R. § 97(f), to enable Applicant to fully comply.

If any fees are due in connection with the filing of this statement, please charge all required fees to Deposit Account No. 50-2212, Order Number 044988.030.8977. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

Date: April 7, 2004

  
Aubrey A. Haddach  
Registration No. 48,374  
PILLSBURY WINTHROP, LLP  
11682 El Camino Real, Suite 200  
San Diego, California 92130-2092  
(858) 847-4189



PTO/SB/08A (08-03)

Approved for use through 07/31/2006. OMB 0651-0031

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1

of 5

### Complete if Known

Application Number	Not yet assigned
Filing Date	April 7, 2004
First Named Inventor	Pantoliano et al.
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	044988-0308977

### U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
	1	US- 4,580,895	04-08-1986	PATEL	
	2	US- 4,626,684	12-02-1986	LANDA	
	3	US- 4,628,026	12-09-1986	GARDELL et al.	
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Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T <sup>4</sup>
		Country Code <sup>3</sup> Number <sup>4</sup> Kind Code <sup>5</sup> (if known)				
	20	EP 0 512 334	11-1992			
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		Filing Date	April 7, 2004
		First Named Inventor	Pantoliano et al.
		Art Unit	Not yet assigned
		Examiner Name	Not yet assigned
		Attorney Docket Number	044988-0308977
Sheet	2	of	5

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